

Long-Lasting Drop in Perfusion of a Non-small Cell Lung Cancer Induced by Monotherapy with the Epithelial Growth Factor Receptor Inhibitor Erlotinib Persisting Despite Tumor Progression at Remote Sites

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A 56-year-old woman was diagnosed at our hospital with G2 adenocarcinoma of the lung (T3, N2, M1) metastatic to the brain. Subsequently, first-line therapy with gemcitabine and cisplatin and whole-brain radiation therapy were initiated. Because of therapy-related hardness of hearing, cisplatin had to be replaced by carboplatin after two therapy cycles. After 4 months, tumor progression was diagnosed by computed tomography (CT), and consequently, third-line therapy with EGFR tyrosine kinase inhibitor erlotinib was initiated. Contrast-enhanced CT performed at this time included additional volume perfusion measurement of the primary tumor (Figure 1, upper panel). Longest tumor diameter recorded was 73.6 mm, whereas automatically determined blood flow (BF), blood volume (BV), and vessel wall permeability (PMB) in the primary tumor yielded 56/18.5/9.5 ml/100 ml tissue/min, respectively. Eight weeks later, during ongoing therapy, repeated CT volume perfusion showed neither significant tumor size change (longest diameter, 70.5 mm) nor signs of tumor spread, but a marked drop in BF (28.4 ml/100 ml tissue/min), BV (10.5 ml/100 ml tissue/min), and PMB (10.5 ml/100 ml tissue/min) assumed to represent antiangiogenic switch induced by erlotinib therapy (Figure 1, middle panel). Another 12 weeks later, there was still no significant change in tumor size (current longest diameter, 70.7 mm) but further reduction of tumor perfusion parameters, BF (27 ml/100 ml tissue/min) and BV (4.5 ml/100 ml tissue/min), whereas PMB (18 ml/100 ml tissue/min) increased (Figure 1, lower panel). However, whole-body CT disclosed, at this time, new osseous metastases in the cervical spine indicating tumor progression (progressive disease), despite ongoing decrease of tumor perfusion parameters.

Inhibitors of the EGFR tyrosine kinase have clinical efficacy when given as second- or third-line therapy for advanced NSCLC.¹ Knowingly, tumor size measurements, irrespective of their accuracy (uni-bidimensional or computer-assisted volum-

etry), are not expected to objectively reflect response to treatment, at least early after treatment onset.^{2,3} However, because of erlotinib impact on tumor angiogenesis, perfusion measurements represent a reliable surrogate parameter capable of confirming early response to EGFR inhibitors.⁴ Thus, preliminary results of clinical-radiologic trials focusing on noninvasive quantification of blood flow parameters by using dynamic contrast-enhanced perfusion CT proved successful in demonstrating decreasing effects of different angiogenesis inhibitors on tumor blood flow parameters.

Herein, we present serial measurements of tumor volume and tumor perfusion in a patient with NSCLC receiving monotherapy with erlotinib, using a new CT volume perfusion technique, which is able to noninvasively assess blood flow parameters (BF, BV, and PMB). This technique uses rapid table movement, robust motion correction, and low-dose energy parameters, thus overcoming classic sampling errors that were inherent in earlier tumor perfusion protocols addressing only limited tumor regions (slices) caused by technical CT limitations. Perfusion analysis of the primary tumor in our patient expectedly demonstrated marked decrease in tumor perfusion during erlotinib therapy persisting even after tumor progression was confirmed at other sites. Interestingly, tumor size did not change significantly at follow-up, which is going along with current data regarding the impact of targeted therapies on tumor volume.

Therefore, acquisition of functional data is imperative in these cases. However, they only represent a useful adjunct to whole-body investigational protocols, which are still required for correct evaluation of the course of the disease.

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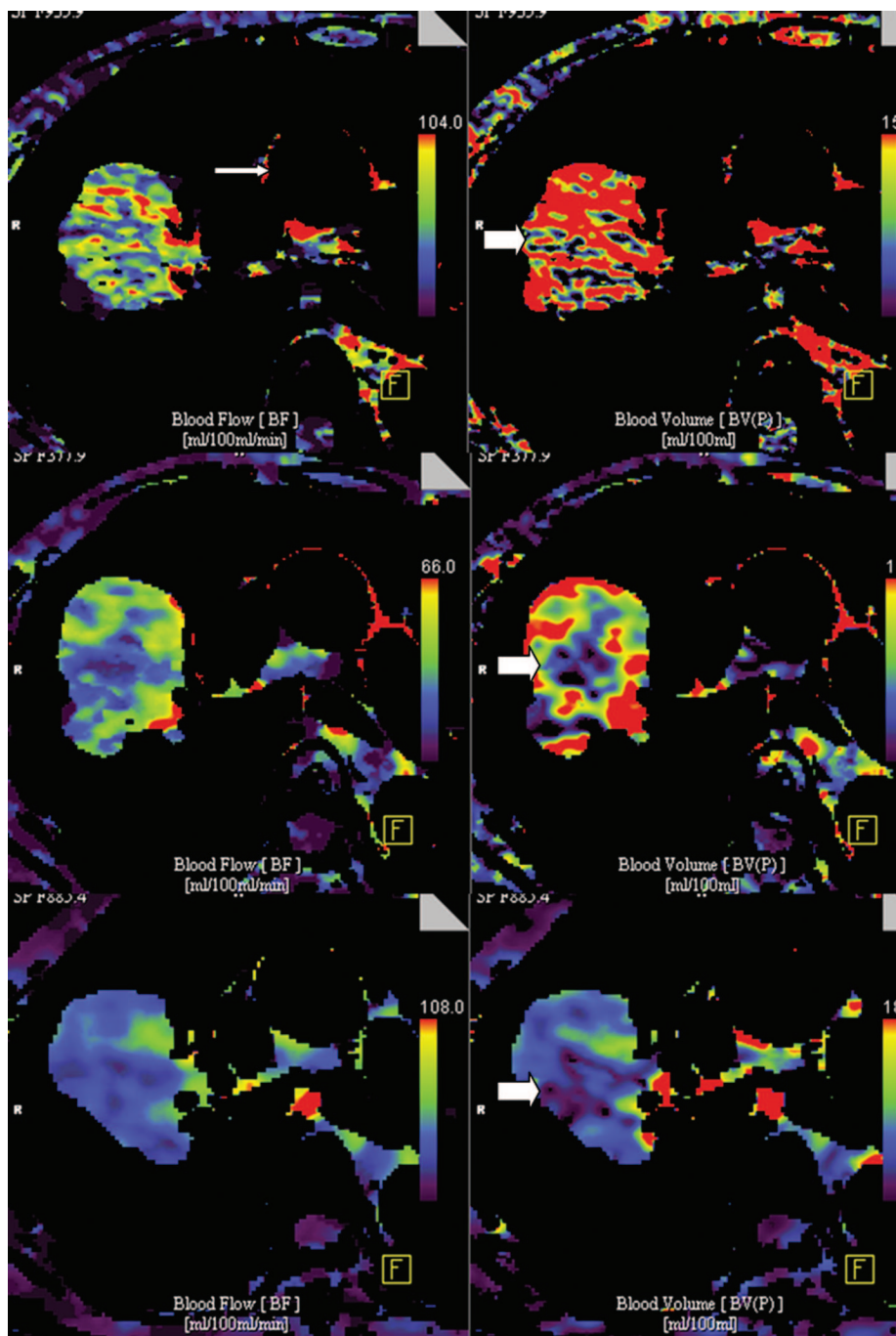


FIGURE 1. Axial contrast-enhanced computed tomography examinations of the chest displaying a large bronchial carcinoma in the right upper lobe at the level of the ascending aorta (long arrow, left upper panel). At baseline (upper row), color maps reflecting BF and BV demonstrated nearly homogeneous (arrow), strong tumor perfusion (micro vessel density) with no macroscopic necrosis. The color scale at the right side shows perfusion intensity declining from the top (red) to the bottom (violet). At the first follow-up (middle panel), erlotinib-induced hypoperfusion of the tumor core is seen (arrow). At the second follow-up (lower panel), perfusion CT disclosed almost global hypoperfusion of the mass (arrow) after ongoing erlotinib therapy. Note that tumor size did not change significantly with time.